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MAJOR ARTICLE

Impact of Initial Antifungal Therapy on the Outcome of Patients With Candidemia and Septic Shock Admitted to Medical Wards: A Propensity Score–Adjusted Analysis

Marco Falcone,[1] Giusy Tiseo,[1] Belen Gutiérrez-Gutiérrez,[2] Giammarco Raponi,[3] Paolo Carfagna,[4] Chiara Rosin,[5] Roberto Luzzati,[5] Diego Delle Rose,[6] Massimo Andreoni,[6] Alessio Farcomeni,[3] Mario Venditti,[3] Jesus Rodríguez-Baño,[2] and Francesco Menichetti[1]; for GISA (Italian Group for Antimicrobial Stewardship)

[1]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy; [2]Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen Macarena/Departamento de Medicina, Universidad de Sevilla/Instituto de Biomedicina de Sevilla (IBiS), Sevilla, Spain; [3]Department of Public Health and Infectious Diseases, "Sapienza" University of Rome, Rome, Italy; [4]San Giovanni Addolorata Hospital, Rome, Italy; [5]University Hospital of Trieste, Trieste, Italy; [6]Clinical Infectious Diseases, Department of Systems Medicine, Tor Vergata University, Rome, Italy

Background. Echinocandins are recommended as firstline therapy in patients with candidemia. However, there is debate on their efficacy in survival outcomes. The aim of this study is to evaluate whether the choice of initial antifungal therapy improves mortality in patients with candidemia in relation to the presence of septic shock.

Methods. Patients with candidemia hospitalized in internal medicine wards of 5 tertiary care centers were included in the study (December 2012–December 2014). Patient characteristics, therapeutic interventions, and outcome were reviewed. Propensity score (PS) was used as a covariate of the multivariate analysis to perform a stratified analysis according to PS quartiles and to match patients receiving "echinocandins" or "azoles."

Results. Overall, 439 patients with candidemia were included in the study. A total of 172 (39.2%) patients had septic shock. Thirty-day mortality was significantly higher in patients with septic shock (45.3%) compared with those without septic shock (31.5%; $P = .003$). Among patients with septic shock, the use of echinocandins in the first 48 hours, compared with azoles, did not affect 30-day mortality in the PS-adjusted Cox regression analysis (hazard ratio [HR], 0.77; 95% confidence interval [CI], 0.37–1.59; $P = .48$), the PS-stratified analysis, or the logistic regression model in matched cohorts (adjusted HR, 0.92; 95% CI, 0.51–1.63; $P = .77$).

Conclusions. Echinocandin therapy seems not to improve the outcome of non–intensive care unit patients with septic shock due to candidemia. These findings support the urgent need of further studies in this patient population.

Keywords. candidemia; early antifungal therapy; echinocandins; septic shock.

In the last decade, *Candida* spp. has been recognized as the fourth most common cause of nosocomial bloodstream infection (BSI) [1, 2]. Despite the identification of risk factors for candidemia, the development of prediction rules for different patient populations, and advances in early diagnosis and treatment, candidemia is still responsible for high costs, prolonged length of stay, and increased mortality rates [3–5]. Mortality is particularly high among patients with septic shock [6].

Current guidelines for the management of candidemia recommend an echinocandin as firstline therapy, confining the use of fluconazole as initial therapy only in patients who are not critically ill [7]. However, no study has evaluated the impact of different antifungal agents on the outcome of patients with different clinical presentations, in particular among non-neutropenic patients with septic shock admitted to medical wards.

The aim of this study is to evaluate whether initial therapy with echinocandins improves mortality in patients with candidemia in relation to the presence of septic shock.

METHODS

Study Population and Study Design

This multicenter observational study was performed in 5 tertiary care hospitals located in different regions in Italy:

- Hospital 1: Policlinico Umberto I, "Sapienza" University, Rome (1100 beds)
- Hospital 2: San Giovanni-Addolorata Hospital, Rome (700 beds)

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Correspondence: M. Falcone, MD, Division of Infectious Diseases, Department of Clinical and Experimental Medicine, University of Pisa, Via Paradisa 2, Pisa, 56124- Italy (marco.falcone@unipi.it).

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- Hospital 3: University Hospital of Trieste (840 beds)
- Hospital 4: Azienda Ospedaliera Universitaria Pisana, Pisa (1000 beds)
- Hospital 5: University Tor Vergata, Rome (460 beds)

The study included cases observed from December 2012 to December 2014 in the internal medicine wards (IMWs) of the participating sites. Hospitalized patients aged ≥18 years with a definite diagnosis of candidemia were included in the study. Candidemia was defined by at least 1 positive blood culture yielding *Candida* spp. in a patient with fever and/or other clinical signs of infection [8]. Exclusion criteria were age <18 years, neutropenia (defined as absolute neutrophil count $<0.5 \times 10^9$/L or expected to fall below 0.5×10^9/L) and presence of hematological malignancy [9]. According to the study protocol, patients with candidemia hospitalized in nonmedical wards (surgery or intensive care unit [ICU]) were not included in the study. However, patients initially hospitalized in medical wards who were transferred to the ICU after diagnosis of candidemia were included in the analysis. The local ethics committees approved the study in each center. According to local and national policies, informed consent was waived for this type of study.

Data Collection and Study Definitions

Demographic data, underlying diseases, reasons for hospital admission, and severity of illness of patients with definite diagnosis of candidemia were retrospectively reviewed on a standardized report form. The variables considered were age, sex, underlying diseases, weight of comorbidities assessed by the Charlson comorbidity index, presence of intravascular devices, such as central venous catheter (CVC) or peripherally inserted central catheter (PICC), administration of total parenteral nutrition (TPN) [10], surgery in the previous 30 days, and hospitalization in the previous 3 months. Previous antibiotic therapy, a recognized risk factor for candidemia [11], was defined as exposure to antibiotics for at least 48 hours in the 30 days preceding candidemia. The administration of a concomitant antibiotic (defined as exposure to antibiotics within 48 hours before diagnosis of candidemia) and immunosuppressive therapy (defined as use of steroids [prednisolone >0.5 mg/kg/d or equivalent for >1 month], chemotherapy, or anti–tumor necrosis factor therapy within the past 3 months) were also reported.

Clinical variables (including presence of fever, vital signs, need for intensive support or vasopressors) were assessed at the onset of candidemia. The onset of candidemia was defined as the time of the onset of signs of infection (2 or more of the following: fever, tachycardia, hypotension, reduced urine output, altered mental status, or an increase of SOFA score ≥2 from baseline). According to Sepsis-3 criteria, the presence of septic shock was defined as the requirement of a vasopressor to maintain a mean arterial pressure of ≥65 mmHg and a serum lactate level >2 mmol/L (>18 mg/dL) in the absence of hypovolemia [12, 13].

Data about the administration of the initial antifungal therapy were collected. Initial antifungal therapy defined as an antifungal treatment administered within 48 hours of the blood culture being taken [14, 15, 17]; the following regimens were identified: (i) azole, if the patient received fluconazole or voriconazole; (ii) echinocandins, if 1 of the 3 available echinocandins (caspofungin, anidulafungin, micafungin) was administered; or (iii) amphotericin B. In all the centers involved in the study, the choice of antifungal therapy (drug and dosages) was driven by an infectious disease consultant.

Data from cases with missing treatment information and those who received no antifungal therapy within the first 48 hours from the blood cultures collection were excluded from analysis. Sources of candidemia were defined according to US Centers for Disease Control and Prevention definitions [16]. Information about device (CVC or PICC) removal was collected. Source control measures were considered within the first 48 hours of determination of blood culture positivity. These included the removal of CVC or surgical or radiologic procedures to drain abscesses or fluid collections thought to be the source of *Candida* infection [17]. The outcome variable was mortality within 30 days of the onset of candidemia [15].

During the study period, there were no changes in microbiological laboratory techniques in the 5 hospitals. Blood cultures were processed using the automated blood culture system BacT/Alert 3D (Biomérieux Inc., Marcy l'Etoile, France). Confirmation of *Candida* spp. identification was performed by the Vitek-2 system (Biomérieux Inc.). Antifungal susceptibility testing to amphotericin B, echinocandins, and fluconazole was performed using the Sensititre YeastOne colorimetric plate (TREK Diagnostic Systems, Cleveland, OH). The interpretive breakpoints were those proposed in the CLSI (formerly the NCCLS) M44-A reference method [18].

This study is reported following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [19].

Study End Point and Statistical Analysis

The aim of the study is to evaluate whether the initial administration of echinocandins improved 30-day survival in patients affected by candidemia with septic shock compared to those without septic shock.

To achieve this goal, a comparison between candidemic patients who received echinocandins and patients who received azoles within the first 48 hours after the collection of blood cultures has been performed in both the groups of patients with and without septic shock. Continuous variables were compared by the Student *t* test if normally distributed and the Mann-Whitney *U* test if non-normally distributed. Categorical

variables were evaluated using the χ^2 or the 2-tailed Fisher exact test. Values for continuous and categorical variables are expressed as the mean ±SD or median (interquartile range [IQR]) and percentage of the group from which they are derived, respectively.

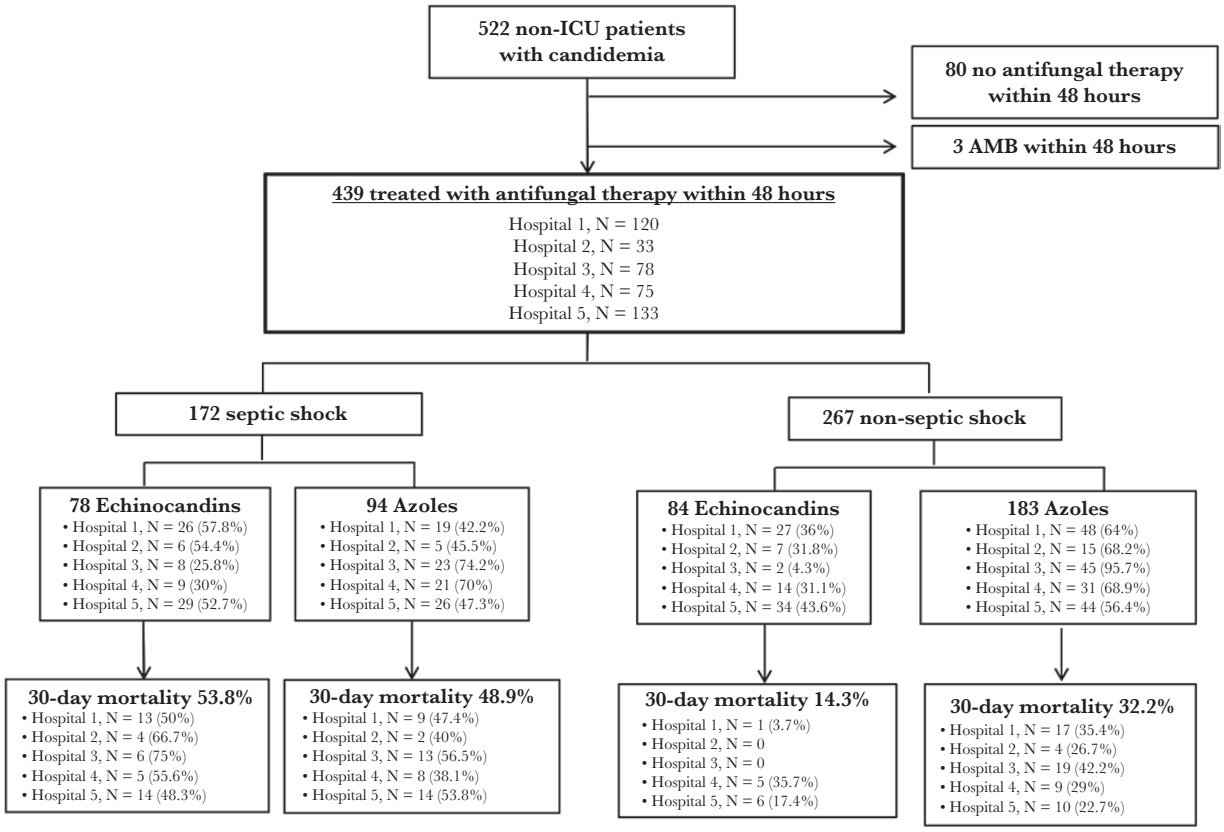
Separate analyses were performed for the 2 cohorts (septic shock vs no septic shock). A propensity score (PS; the probability of receiving empirical therapy with echinocandin) was calculated for each cohort; all the models obtained for PS had an area under the receiver operating characteristic curve (AUROC) of ≥0.80. The PS was used in 3 ways: (i) as a covariate in multivariate analysis; (ii) to stratify the cohorts according to quartiles of the PS; and (iii) to match patients so that each patient who received empirical treatment with an echinocandin was matched with 1 who received treatment with an azole using calipers of a width equal to 0.2 of the SD of the logit of the propensity score. We calculated the variance inflation factor value for every variable included to control for the potential occurrence of collinearity between the variables included to calculate the PS. Multivariate analyses for mortality at day 30 were performed using logistic regression to control for confounding. We compared mortality in matched pairs with conditional logistic regression. Odds ratios (ORs) or hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated when logistic and Cox regression analysis were used, as appropriate. Charlson comorbidity index was used as a dichotomic variable (Charlson >8 and ≤8) according to Classification and Regression Tree (CART) analysis.

To control for the site effect, we classified centers into those with low (low–mortality risk centers) and high (high–mortality risk centers) mortality using TreeNet considering all other variables; therefore, sites classified as high-risk centers were those with high mortality after consideration of patients' features.

Statistical significance was established at ≤.05. All reported *P* values are 2-tailed. The results obtained were analyzed using commercially available statistical software packages (SPSS, version 20.0; SPSS, Inc., Chicago, IL; and R, versions 3.0.2 and 3.5.1; R Development Core Team, Vienna, Austria).

RESULTS

During the study period, a total of 522 episodes of candidemia were included in the study. Eighty patients did not receive an



Hospital 1 = Policlinico Umberto I, Rome; Hospital 2 = San Giovanni Addolorata hospital, Rome; Hospital 3 = University Hospital of Trieste; Hospital 4 = Azienda Ospedaliera Universitaria Pisana, Pisa; Hospital 5 = University Tor Vergata, Rome.

Figure 1. Flowchart of cases of candidemia in non–intensive care unit patients in the 5 study centers. Abbreviations: ICU, intensive care unit.

antifungal therapy within 48 hours; among these patients, the median time from candidemia to death (IQR) was 3 (2–6) days. All these patients were excluded from the final analysis (Figure 1). Three (0.7%) patients received amphotericin B and were excluded from the final analysis. Of the remaining 439 patients, 162 (36.9%) received an echinocandin and 277 (63.1%) received azoles within 48 hours of the collection of blood cultures (Figure 1).

Of the 439 patients included in the analysis, 172 (39.2%) patients had candidemia with septic shock at presentation, with a 30-day mortality rate of 51.2%. Among the remaining 267 patients, the 30-day mortality rate was 26.6%. Table 1 shows the baseline clinical and demographic characteristics of patients by severity group (septic shock vs nonseptic shock). The median age (IQR) was similar in patients presenting with septic shock at the time of diagnosis of candidemia (79 [71–86] years) compared with those without septic shock (76 [67–85] years; P = .059). *Candida albicans* was the most frequent isolate (52.7%), followed by *Candida parapsilosis* (21.5%), *Candida tropicalis* (9.9%), *Candida glabrata* (6.8%), *Candida krusei* (2%), and other *Candida* species (5.6%). In 6 patients (1.4%), 2 *Candida* species were isolated. No differences in *Candida* species were observed between the 2 study groups (data not shown).

Patients with septic shock were more frequently treated with antibiotics in the previous 30 days, were more often hospitalized in the previous 3 months, and had more frequently had a PICC inserted. Source control was performed more frequently in patients with septic shock. With regards to therapy, the majority of patients without septic shock received azoles as initial therapy (68.5%). Conversely, patients with septic shock more frequently received an echinocandin as initial therapy (45.3% vs 31.5%; P = .003).

Table 2 shows the comparison between candidemic patients who received vs did not receive echinocandin therapy according to the presence of septic shock. Among nonseptic patients, those receiving echinocandins had a lower 30-day mortality compared with patients receiving other antifungals (14.3% vs 32.2%; P = .002), whereas no differences in mortality were observed in patients presenting with septic shock (53.8% vs 48.9%; P = .521). High-mortality risk centers were the Hospital of Trieste in patients with septic shock and Policlinico Umberto I and Hospital of Trieste in those without septic shock (Supplementary Figures 1 and 2).

Table 1. Clinical Features and Outcomes of Patients With Candidemia Presenting With and Without Septic Shock

	Patients With Candidemia n = 439		
	Patients With Septic Shock	Patients Without Septic Shock	
	n = 172	n = 267	*P* Value
Male	78 (45.3%)	125 (46.8%)	.763
Age, median (IQR), y	79 (71–86)	76 (67–85)	.059
Diabetes mellitus	79 (45.9%)	130 (48.7%)	.572
Chronic renal failure	49 (28.5%)	72 (27%)	.728
COPD	53 (30.8%)	78 (29.2%)	.721
Solid cancer	41 (23.8%)	55 (20.6%)	.423
IBD	4 (2.4%)	11 (4.1%)	.323
Previous surgery (30 d)	22 (12.8%)	31 (11.6%)	.711
Previous hospitalization (90 d)	65 (37.8%)	66 (24.7%)	*.003*
Previous antibiotic therapy (30 d)	129 (75%)	170 (63.7%)	*.013*
Concomitant antibiotic therapy	89 (51.7%)	182 (68.2%)	*.001*
Immunosuppressive therapy	79 (45.9%)	101 (37.8%)	.092
Steroids	62 (36%)	73 (27.3%)	.054
CVC	47 (27.3%)	58 (21.7%)	.179
PICC	86 (50%)	104 (39%)	*.023*
TPN	118 (68.6%)	134 (50.2%)	*<.001*
Charlson comorbidity index, median (IQR)	7 (6–8)	7 (6–8)	.176
Fever	100 (58.1%)	124 (46.4%)	*.017*
Source control	99 (57.6%)	126 (47.2%)	*.034*
Transfer to ICU	12 (7%)	7 (2.6%)	*.029*
Antifungal chemotherapy			
Echinocandins within the first 48 h	78 (45.3%)	84 (31.5%)	*.003*
Azole within the first 48 h	94 (54.7%)	183 (68.5%)	*.003*
30-d mortality	88 (51.2%)	71 (26.6%)	*<.001*

Abbreviations: CVC, central venous catheter; ICU, intensive care units; IQR, interquartile range; PICC, peripherally inserted central catheter; TPN, total parenteral nutrition.

PS analyses in patients with and without septic shock are reported in Supplementary Tables 1 and 2. The PS among patients with septic shock showed a *P* value of .70 for the Hosmer-Lemeshow goodness-of-fit test and an AUROC of 0.80 (95% CI, 0.74–0.87), whereas the PS among patients without septic shock showed a *P* value of 0.48 for the Hosmer-Lemeshow goodness-of-fit test and an AUROC of 0.81 (95% CI, 0.76–0.86).

Univariate analysis of variables associated with 30-day mortality in both cohorts of patients is shown in Supplementary Table 3. Multivariate (logistic and Cox regression) analysis of mortality at day 30 including the PS as covariates in both study groups is shown in Table 3A and B. The PS-adjusted OR of echinocandin for 30-day mortality was 0.77 (95% CI, 0.37–1.59; *P* = .48), and the PS-adjusted HR of echinocandin for 30-day mortality was 0.79 (95% CI, 0.37–2.11; *P* = .30). Conversely, in patients without septic shock, both logistic and Cox regression models showed that receiving an echinocandin within the first 48 hours was a factor independently associated with lower risk of mortality; when potential confounders were added, the PS-adjusted OR of echinocandin for 30-day mortality was 0.40 (95% CI, 0.18–0.88; *P* = .02) and the PS-adjusted HR was 0.45 (95% CI, 0.22–0.92; *P* = .03). However, in a stratified analysis performed according to the quartiles of the PS (Table 4), no significant differences in 30-day mortality rates between patients receiving echinocandins or azoles were detected in the 2 study groups.

Finally, we performed a PS-based matched analysis; we were able to match 45 couples to patients with septic shock and 63 to those without septic shock. The matched patients did not show significant differences in exposure to variables related to empirical therapy (Supplementary Table 4). Conditional logistic regression in PS-matched cohorts (Table 5) showed that echinocandins within the first 48 hours were associated with 30-day mortality in patients without septic shock (adjusted HR [aHR], 0.43; 95% CI, 0.21–0.91; *P* = .03), but not in those with septic shock (aHR, 0.92; 95% CI, 0.51–1.63; *P* = .77).

DISCUSSION

This multicenter study suggests that, independent of other factors that potentially influence outcome (including early catheter removal), initial echinocandin therapy does not seem to impact the outcome of candidemic patients presenting with septic shock. This finding may have significant clinical implications in the selection of patients who really benefit from echinocandins as initial therapy.

Table 2. Comparison of Candidemic Patients who Received or Not Echinocandins According to the Presence of Septic Shock

	Patients With Candidemia With Septic Shock (n = 172)			Patients With Candidemia Without Septic Shock (n = 267)		
Variables	ECH n = 78	Azoles n = 94	*P* Value	ECH n = 84	Azoles n = 183	*P* Value
Male	38 (47.8%)	40 (42.6%)	.42	37 (44%)	88 (48.1%)	.539
Age, median (IQR), y	75 (67–83)	82.5 (72–89)	*.002*	72 (63–80)	78 (70–87)	*<.001*
Diabetes mellitus	42 (53.8%)	37 (39.4%)	.058	51 (60.7%)	79 (43.2%)	*.008*
Chronic kidney disease	28 (35.9%)	21 (22.3%)	.050	26 (31%)	46 (25.1%)	.320
COPD	24 (30.8%)	29 (30.9%)	.991	17 (20.2%)	61 (33.3%)	*.029*
Solid cancer	18 (23.1%)	23 (24.5%)	.831	10 (11.9%)	45 (24.6%)	*.017*
IBD	2 (2.6%)	2 (2.2%)	.848	4 (4.8%)	7 (3.8%)	.721
Candida albicans or *tropicalis*	46 (59%)	62 (66%)	.346	55 (65.5)	113 (61.7)	.560
Previous surgery (30 d)	11 (14.1%)	11 (11.7%)	.639	13 (15.5%)	18 (9.8%)	.182
Previous hospitalization (90 d)	28 (35.9%)	37 (39.4%)	.641	15 (17.9%)	52 (27.9%)	.078
Previous antibiotic therapy (30 d)	64 (82.1%)	65 (69.1%)	.052	51 (60.7%)	119 (65%)	.496
Immunosuppressive therapy	38 (48.7%)	41 (43.6%)	.504	31 (36.9%)	70 (38.3%)	.833
Steroids	27 (34.6%)	35 (37.2%)	.722	18 (21.4%)	55 (30.1%)	.142
Chemotherapy	12 (15.4%)	9 (9.6%)	.247	4 (4.8%)	15 (8.2%)	.311
CVC	17 (21.8%)	30 (31.9%)	.138	11 (13.1%)	47 (25.7%)	*.021*
PICC	32 (41%)	54 (57.4%)	*.032*	33 (39.3%)	71 (38.8%)	.939
TPN	49 (62.8%)	69 (73.4%)	.137	38 (45.2%)	96 (52.5%)	.273
Source control	33 (42.3%)	66 (70.2%)	*.001*	37 (44%)	89 (48.6%)	.486
Charlson comorbidity index, median (IQR)	7 (5–8)	7 (6–8)	.287	6 (4–8)	7 (6–8)	*.041*
Fever	42 (53.8%)	58 (61.7%)	.298	29 (34.5%)	95 (51.9%)	*.008*
Transfer to ICU	5 (6.4%)	7 (7.4%)	.791	6 (7.1%)	1 (0.5%)	*.002*
Targeted therapy with echinocandins	69 (88.5%)	14 (14.9%)	<.001	74 (88.1%)	11 (6%)	*<.001*
High-risk center	8 (10.3%)	23 (24.5%)	.02	29 (34.5%)	93 (50.8%)	*.01*
30-d mortality	42 (53.8%)	46 (48.9%)	.521	12 (14.3%)	59 (32.2%)	*.002*

Abbreviations: CVC, central venous catheter; ECH, echinocandins; ICU, intensive care units; IQR, interquartile range; PICC, peripherally inserted central catheter; TPN, total parenteral nutrition.

Table 3. Logistic Regression (A) and Cox Regression (B) Analysis of 30-Day Mortality Including the Propensity Scores as Covariates in Patients With and Without Septic Shock

A

	Patients With Septic Shock[a]		Patients Without Septic Shock[b]	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Empirical echinocandins	0.77 (0.37–1.59)	.48	0.40 (0.18–0.88)	.02
Antibiotic therapy previous 30 d			0.49 (0.27–0.90)	.02
Charlson index >8			0.39 (0.17–0.86)	.02
Candida albicans or *tropicalis*			1.77 (0.94–3.34)	.07
Chemotherapy			4.48 (1.29–15.60)	.02
Chronic renal failure			1.78 (0.91–3.49)	09
Propensity score	0.65 (0.16–2.63)	.54	0.18 (0.04–0.88)	.04

B

	Patients With Septic Shock		Patients Without Septic Shock	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Empirical echinocandins	0.79 (0.37–2.11)	.30	0.45 (0.22–0.92)	.03
Antibiotic therapy previous 30 d			0.56 (0.34–0.91)	.02
Charlson index >8			0.41 (0.21–0.82)	.01
Chemotherapy			1.91 (0.90–4.03)	.09
Chronic renal failure			1.89 (1.10–3.23)	.02
Propensity score	0.70 (0.26–1.87)	.48	0.31 (0.09–1.11)	.07

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IBD, inflammatory bowel disease; ICU, intensive care unit; ROC, receiver operating characteristics.

[a]Variables used for calculating the propensity score in the septic shock cohort: sex, age, hospital, ward of hospitalization, antibiotic therapy in prior 30 days, surgery in prior 30 days, hospitalization in prior 90 days, total parenteral nutrition, chronic renal failure, steroids, COPD, chemotherapy, diabetes, solid cancer, IBD, presence at least 2 comorbidities, Charlson >8, source control, fever, transfer to ICU. The area under the ROC curve for the propensity score was 0.80.

[b]Variables used for calculating the propensity score in nonseptic shock cohort: sex, age, hospital, ward of hospitalization, antibiotic therapy in prior 30 days, surgery in prior 30 days, hospitalization in prior 90 days, total parenteral nutrition, chronic renal failure, steroids, COPD, chemotherapy, diabetes, solid cancer, IBD, presence at least 2 comorbidities, Charlson >8, fever, transfer to ICU. The area under the ROC curve for the propensity score was 0.81.

The efficacy of echinocandins in improving the outcome of patients with candidemia is still debated. Current Infectious Diseases Society of America guidelines on the management of candidemia in non-neutropenic patients recommend the use of an echinocandin as initial therapy in unstable patients, whereas fluconazole is considered an acceptable alternative in selected patients, including those who are not critically ill and who are considered unlikely to have a fluconazole-resistant *Candida* species [7]. However, no randomized clinical trials have clearly demonstrated the superiority of echinocandins compared with a comparator in the treatment of candidemia in non-neutropenic adult patients [20–22]. Although Reboli

Table 4. Stratified Analysis of 30-Day Mortality of Patients With or Without Septic Shock Treated With Echinocandins or Azoles Within the First 48 Hours, According to Quartiles of the Propensity Score

Propensity Score Quartiles	With Septic Shock[a]			Propensity Score Quartiles	Without Septic Shock[b]		
Propensity Score Range	ECH n = 78	Azoles n = 94	*P*	Propensity Score Range	ECH n = 84	Azoles n = 183	*P*
1st (0.03–0.228)	4/6 (66.7)	20/37 (54.0)	.564	1st (0.03–0.108)	0/2 (0)	26/65 (40.0)	.253
2nd (0.232–0.440)	8/15 (53.3)	12/28 (42.9)	.512	2nd (0.110–0.282)	1/15 (6.7)	16/52 (30.8)	.059
3rd (0.448–0.652)	12/24 (50.0)	8/19 (42.1)	.606	3rd (0.284–0.471)	3/23 (13.8)	11/43 (23.2)	.235
4th (0.677–0.964)	18/33 (54.5)	6/10 (60.0)	.761	4th (0.475–0.982)	8/44 (18.2)	6/23 (26.1)	.450
Total	42/78 (53.8)	46/94 (48.9)	.521	Total	12/84 (14.3)	59/183 (32.2)	.002

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; IBD, inflammatory bowel disease; ICU, intensive care unit; ROC, receiver operating characteristics.

[a]Variables used for calculating the propensity score in the septic shock cohort: sex, age, hospital, ward of hospitalization, antibiotic therapy in prior 30 days, surgery in prior 30 days, hospitalization in prior 90 days, total parenteral nutrition, chronic renal failure, steroids, COPD, chemotherapy, diabetes, solid cancer, IBD, presence at least 2 comorbidities, Charlson >8, source control, fever, transfer to ICU. The area under the ROC curve for the propensity score was 0.80.

[b]Variables used for calculating the propensity score in nonseptic shock cohort: sex, age, hospital, ward of hospitalization, antibiotic therapy in prior 30 days, surgery in prior 30 days, hospitalization in prior 90 days, total parenteral nutrition, chronic renal failure, steroids, COPD, chemotherapy, diabetes, solid cancer, IBD, presence at least 2 comorbidities, Charlson >8, fever, transfer to ICU. The area under the ROC curve for the propensity score was 0.81.

Table 5. Conditional Logistic Regression in Propensity Matched Cohorts

	Patients With Septic Shock		Patients Without Septic Shock	
	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Empirical echinocandins	0.92 (0.51–1.63)	.77	0.43 (0.21–0.91)	.03

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

et al. [20] demonstrated that the global response at the end of treatment was significantly higher in patients treated with anidulafungin than in those who received fluconazole, no differences in 14- and 28-day mortality between the 2 study groups were demonstrated in a secondary post hoc analysis of this trial [23]. A prospective study on patients with candidemia admitted to IMWs found no differences in mortality rates between those starting with fluconazole or echinocandin, with an unexpected slightly worse survival in those who received echinocandins than the other groups [24]. Furthermore, a recent prospective, population-based cohort study on candidemia in Spanish hospitals showed that both empirical and targeted treatment with fluconazole was not associated with increased 30-day mortality compared with echinocandins [14].

Our findings suggest that, compared with azole therapy (mainly fluconazole therapy), echinocandins are not associated with improved mortality in non-ICU patients hospitalized in medical wards with septic shock due to candidemia. Several reasons may explain these findings. Patients hospitalized in IMWs are usually old, with severe rapidly fatal comorbidities, and they frequently lack the distinctive signs of systemic infections (eg, fever) [25]. This factor might, in part, justify the high mortality recorded in our patients, especially in those without septic shock, in whom it is more difficult to detect the presence of an infection. Furthermore, among septic patients, echinocandin exposure seems to be lower than in healthy volunteers [26–28], and patients with severe hypoalbuminemia have lower plasma trough levels of echinocandins [29]. Considering the rather frequent occurrence of malnutrition and severe hypoalbuminemia in the elderly [30], all these findings justify pharmacokinetic studies of the 3 echinocandins in this patient population. Finally, we recorded a high mortality rate among patients without septic shock receiving fluconazole (32.2%) vs those receiving echinocandins (14.2%; $P = .002$). This latter observation can be explained in several ways: (i) some relevant confounders may not have been measured in the group of patients without shock (eg, use of fluconazole in patients with terminal cancer was not well assessed by the Charlson comorbidity index); (ii) it is not known if azoles were used intravenously in all cases and if a loading dose was administered; (iii) data about minimum inhibitory concentrations for antifungals were not available for all the cases.

Our study has some limitations. The observational nature of the study is the major limitation of the study. Furthermore, the confidence intervals of the estimation (effect of echinocandin therapy in patients with septic shock) are wide, and the power to detect a difference can be limited. Moreover, other variables, such as prompt fluid resuscitation, use of vasopressors, efficacious control of hypoxemia, and serum lactate levels, can influence the prognosis of patients with septic shock. Thus, in this population, it is difficult to identify a unique factor that influences mortality. However, our study is consistent with real clinical practice and offers an objective evaluation of patients with candidemia septic shock hospitalized in IMWs. A strength of this study is the large number of patients with candidemia included in the analysis, higher than that of other similar cohorts. Moreover, we performed a PS-adjusted analysis, considering many variables that could potentially influence the outcomes of patients. Finally, our study addresses an important question that could add important information in the controversy about the effect of echinocandins on survival rates. The fact that echinocandins do not impact survival rates over fluconazole in severely ill patients with candidemia and septic shock implies that new diagnostic and treatment strategies are urgently needed in this setting.

CONCLUSIONS

In conclusion, we found that in non-ICU septic patients with candidemia, echinocandins did not improve 30-day survival rates. This finding should not discourage their use in this category of patients as recommended, but it could be the basis for further studies analyzing the factors influencing the response to these drugs. Prevention, early recognition, and management of patients at high risk of candidemia before the development of septic shock remain the most cost-effective measures to improve the outcome of these patients.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Authors' contributions. M.F. planned and designed the study; G.T., P.C., C.R., R.L., and D.D.R. collected data; G.R. performed microbiological

analysis; A.F. and B.G.G. performed statistical analysis; G.T. and M.F. drafted the manuscript and designed tables and figures; M.F., M.A., M.V., and J.R.B. reviewed the final version of the manuscript for intellectual content.

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